

REMARKS

Claims 1-22 are under examination in this case. Claims 19-22 were withdrawn as being directed to a non-elected invention. Claims 3 and 16 stand rejected under 35 U.S.C. § 112, second paragraph; claims 1-18 stand rejected under 35 U.S.C. § 102(b) and 102(e), and claims 10-18 stand rejected under 35 U.S.C. § 103. These rejections are addressed below.

Amendments

Claim 1 has been amended by the incorporation of the limitation of claim 10 (now canceled). Further support for the amendment to claim 1 is found throughout the specification, for example, at page 3, line 27, page 11, lines 13-17, page 13, line 34 to page 14, line 5, and page 22, lines 1-8.

New claims 23-25 were also added to the application. Claim 23 specifies a vector having the additional E-I-S sequence located between the foreign gene and its 5'-flanking gene encoding a viral protein in the negative strand genomic RNA. Support for this claim can be found in the specification, for example, at page 23, Table 1 and in Figure 5. Claim 24 specifies that the additional E-I-S sequence includes the following sequence: 5'-CUUUCACCCU-3'. This claim finds support in the specification, for example, at page 14, lines 27-32. Claim 25 is directed to a composition having at least 4.7×10^8 pfu/ml of a replicable Sendai virus vector of claim 1 in a physiologically acceptable

vehicle. Support for this claim is found in the specification, for example, at page 17, lines 15-24.

No new matter has been added by these amendments.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 3 and 16 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The rejection is based on the term “counting.” In particular, the Examiner raises the question: Does the counting begin at the first residue of the leader sequence or the coding sequence of the genome? This rejection is respectfully traversed. Claim 3 recites “... *the 1st to 6th genes encoding viral proteins, counting from the 3’ end to the 5’ end of the negative strand genomic RNA...*” (emphasis added). Because the leader sequence is required for initiating transcription and is not a gene encoding a viral protein there is no ambiguity as to where the counting begins. In addition, applicants point out that counting from the leader sequence or from the coding sequence should provide the same result. The same is true for claim 16. In short, one skilled in the art would reasonably be apprised of the scope and meaning of the term “counting,” and this rejection should be withdrawn.

Prior Art Rejections

Claims 1-18 stand rejected under 35 U.S.C. § 102(b) as anticipated by Hasan *et al.* (*Journal of General Virology* 78: 2813-2820, 1997). Claims 1-9 stand rejected under 35 U.S.C. §§ 102(b) and (e) as being anticipated respectively by Conzelmann *et al.* (EP 0 702 085 A1) and Conzelmann *et al.* (U.S. Patent No. 6,033,886). Claims 10-18 stand rejected under 35 U.S.C. § 103(a) in view of the Conzelmann references. For the following reasons, these rejections may be withdrawn.

Hasan

Claims 1-18 stand rejected under 35 U.S.C. § 102(b) as anticipated by Hasan *et al.* (*Journal of General Virology* 78: 2813-2820, 1997), with the Examiner stating that “Hasan *et al.* teaches a recombinant Sendai virus that expresses the firefly luciferase gene between the N protein and the 5’ end of the RNA genome.” For the following reasons, this rejection should be withdrawn.

Claim 1, as amended, reads:

A replicable Sendai virus vector carrying a foreign gene that is positioned 5’ to a gene encoding a viral protein in the negative strand genomic RNA contained within said vector, and wherein said RNA comprises an additional E-I-S sequence between said foreign gene and its 5’- or 3’-flanking gene encoding a viral protein.

Hasan fails to describe a vector “carrying a foreign gene that is positioned 5’ to a gene encoding a viral protein in the negative strand genomic RNA contained within said vector” and this reference, therefore, does not teach or suggest applicants’ claimed

invention. Hasan *et al.* appear to show in Figure 1 that the luciferase gene is inserted 5' to the N gene. The described RNA, however, is the sense-strand, namely "antigenomic RNA," which, in turn, is the antisense strand of the genomic RNA of Sendai virus. Once transcribed, the plasmid vector in Figure 1 produces antigenomic RNA. Genomic RNA is then synthesized by L and P proteins using the antigenomic RNA as a template, and the resulting genomic RNA is incorporated into the viral complex. Accordingly, the luciferase gene in Hasan's genomic RNA is positioned to the 3' side of the N gene in the negative strand genomic RNA, namely "upstream" of any viral protein genes ("upstream" refers to the "3'-side" as described in page 11, line 33 of the specification). Accordingly, because Hasan *et al.* does not teach a vector "carrying a foreign gene that is positioned 5' to a gene encoding a viral protein in the negative strand genomic RNA contained within said vector" it cannot anticipate the instant claims, and the rejection should be withdrawn.

The Conzelmann References

Claims 1-9 stand rejected under 35 U.S.C. § 102(b) and 102(e) as anticipated by Conzelmann et al. (EP 0 702 085 A1) and Conzelmann et al. (US Patent No. 6,033,886) respectively, and claims 10-18 stand rejected as obvious in view of these references. For the following reasons, these rejections may be withdrawn.

Applicants first note that, as is indicated above, the claims have been amended to require "a replicable Sendai virus vector." The Conzelmann references do not teach

Sendai virus vectors, as is required by the present claims, and the anticipation rejections of claims 1-9 thus can be withdrawn.

Applicants further note that the pending claims recite that the RNA includes an additional E-I-S sequence between the foreign gene and its 5'- or 3'-flanking gene encoding the viral protein. The Conzelmann references cited in this case do not explicitly teach engineering a vector to include an "additional E-I-S sequence," as now required by the claims. Furthermore, despite the number of vector alterations discussed by Conzelmann, never once do the Conzelmann references suggest introducing an "additional E-I-S sequence" into a paramyxovirus, much less a Sendai virus vector. In short, the Conzelmann references do not support an obviousness rejection of applicants' Sendai virus vectors that include an "additional E-I-S sequence." Accordingly, applicants respectfully request reconsideration on the obviousness rejection in this case and its withdrawal.

In addition, the Conzelmann references, alone or in combination, do not teach or suggest the invention of newly added claims 23-25.

Claim 23 reads:

23. The vector of claim 1, wherein said additional E-I-S sequence is located between said foreign gene and its 5'-flanking gene encoding a viral protein in said negative strand genomic RNA.

Because the Conzelmann references do not teach or suggest an E-I-S sequence, these references cannot describe positioning the additional E-I-S sequence between the foreign

gene and its 5'-flanking gene encoding the viral protein in the negative strand genomic RNA. Applicants, in their specification, constructed viruses having a foreign gene with an additional E-I-S sequence positioned as claimed, and demonstrated that such viral vectors are competent for replication, produce high titers (see page 23, table 1), and express foreign genes to a level at least as shown in Figure 5.

Claim 24 reads:

24. The vector of claim 1 or 23, wherein said additional E-I-S sequence comprises 5'-CUUUCACCCU-3'.

Applicants first note that so-called start ("S") and end ("E") signal sequences play a role in viral gene expression. During transcription of the Sendai virus genome, viral RNA polymerase synthesizes each monocistronic mRNA by recognizing the S and E sequences flanking each gene. E sequences of the Sendai virus are identical for all six viral genes, but there are four (N, P/M/HN, F, and L) different S signals with one or several nucleotide variations.

The virus of claim 24 requires a particular S sequence. This claim is supported by the following description:

...the complementary strand sequence of the Sendai virus S sequence, preferably 5'-CTTTCACCCT-3', the complementary strand sequence of the I sequence, preferably, 5'-AAG-3', the complementary strand sequence of the E sequence, preferably 5'-TTTTTCTTACTACGG-3', is added to the 3' side of the insert fragment... (page 14, lines 27-32, emphasis added)

Because the viral genome is RNA, the sequence, as claimed, is described using RNA-bases: 5'-CUUUCACCCU-3'. Accordingly, as the Conzelmann references do not

disclose or suggest a S sequence, claim 24 cannot be obvious over these references.

Claim 25 reads:

25. A composition comprising at least 4.7×10^8 pfu/ml of the replicable Sendai virus vector of claim 1 in a physiologically acceptable vehicle.

Claim 25 recites a composition having at least 4.7×10^8 pfu/ml of a replicable Sendai virus vector of claim 1 in a physiologically acceptable vehicle. Support for this claim is found, for example, in Table 1, at page 23, where each virus was recovered having a titer of at least 4.7×10^8 pfu/ml. Support is also found in the specification, for example, at page 17, lines 15-24:

The recombinant Sendai viral vector of the invention can be made into a composition by diluting suitably using, for example, physiological saline and PBS, etc. When the recombinant viral vector of the invention is proliferated within hen-eggs, chorioallantoic fluid can also be contained. A composition comprising the recombinant viral vector of the invention may also contain a vehicle such as deionized water, 5% dextrose solution, and such physiologically acceptable vehicles. Furthermore, other than these, stabilizers, pesticides, and such may also be contained. (Emphasis added.)

Applicants note that the Conzelmann references, either alone or in combination, do not teach such high-titer, viral compositions, and these references therefore cannot render the claim obvious.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested.

Applicants note that the Form PTO-1449 that was submitted with an Information Disclosure Statement filed on May 24, 2002 has not been initialed and returned, and hereby request that it be initialed and returned with the next Office action.

Applicant further notes that the Office action was mailed to the incorrect address. Effective immediately, please address all communication in this application to:

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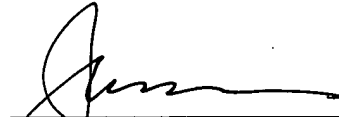
Enclosed is a petition to extend the period for replying for three months, to and including February 18, 2003; February 16th and 17th being a Sunday and federal holiday, respectively.

If there are any charges, or any credits, please apply them to Deposit Account No.

03-2095.

Respectfully submitted,

Date: 18 February 2003



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PATENT TRADEMARK OFFICE

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Version of Claims Showing Changes Made

Claims 1, 2, 4, and 8 have been amended as follows.

1. (Twice amended) A replicable [paramyxovirus] Sendai virus vector carrying a foreign gene that is [located downstream of] positioned 5' to a gene encoding a viral protein in the negative strand genomic RNA contained within said vector, [wherein said vector is capable of expressing said foreign gene] and wherein said RNA comprises an additional E-I-S sequence between said foreign gene and its 5'- or 3'-flanking gene encoding a viral protein.

2. (Twice amended) [A replicable paramyxovirus] The vector of claim 1, wherein said vector is selected from the group consisting of the vectors of (a) to (f) below,

(a) a vector in which the foreign gene is inserted between the 1st gene encoding a viral protein and the 2nd gene encoding a viral protein from the 3' end of the negative strand genomic RNA contained within the vector;

(b) a vector in which the foreign gene is inserted between the 2nd gene encoding a viral protein and the 3rd gene encoding a viral protein from the 3' end of the negative strand genomic RNA contained within the vector;

(c) a vector in which the foreign gene is inserted between the 3rd gene encoding a viral protein and the 4th gene encoding a viral protein from the 3' end of the negative strand genomic RNA contained within the vector;

(d) a vector in which the foreign gene is inserted between the 4th gene encoding a viral protein and the 5th gene encoding a viral protein from the 3' end of the negative strand genomic RNA contained within the vector;

(e) a vector in which the foreign gene is inserted between the 5th gene encoding a viral protein and the 6th gene encoding a viral protein from the 3' end of the negative strand genomic RNA contained within the vector; and

(f) a vector in which the foreign gene is inserted between the 6th gene encoding a viral protein from the 3' end of the negative strand genomic RNA contained within the vector, and the 5' end of said negative strand genomic RNA.

4. (Twice amended) An isolated DNA corresponding to (a) the negative strand genomic RNA contained in the [paramyxovirus] vector of claim 1 or (b) the complementary RNA of said negative strand genomic RNA.

8. (Amended) A vector DNA carrying the DNA of [any one of claims 4 to 7] claim 4 in an expressible manner.

The following new claims (23-25) have been added:

--23. (New) The vector of claim 1, wherein said additional E-I-S sequence is located between said foreign gene and its 5'-flanking gene encoding a viral protein in said negative strand genomic RNA.

24. (New) The vector of claim 1 or 23, wherein said additional E-I-S sequence comprises 5'-CUUUCACCCU-3'.

25. (New) A composition comprising at least 4.7×10^8 pfu/ml of the replicable Sendai virus vector of claim 1 in a physiologically acceptable vehicle. --